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ORIGINAL ARTICLE

Initial cardiovascular treatment patterns during the first 90 days following an incident cardiovascular event

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Aims: The aim of this study was to investigate the initial cardiovascular prescription patterns in patients after their first cardiovascular events, and to identify factors associated with cardiovascular polypharmacy.

Methods: This was a cross-sectional study including patients aged ≥ 45 years with the first record of coronary heart disease (CHD) or stroke between 2007 and 2016 using The Health Improvement Network database. This study investigated the patterns of cardiovascular drugs prescribed during the first 90 days after the first cardiovascular events. Logistic regression was used to examine the association between patients' baseline characteristics and cardiovascular polypharmacy (≥5 cardiovascular drugs).

Results: A total of 121,600 (59,843 CHD and 61,757 stroke) patients were included in the study. The mean age was 69.5 ± 11.9 years. The proportion of patients who were prescribed 0–1, 2–3, 4–5 drugs and ≥6 drugs were 11.0%, 29.8%, 38.6% and 20.5%, respectively. Factors associated with cardiovascular polypharmacy were sex (female: OR 0.74, 95% CI 0.72–0.76 *vs* male), age (75–84 years old: OR 0.50, 0.47–0.53 *vs* 45–54 years old), smoking status (current smoking: OR 1.29, 1.15–1.24 *vs* never), body mass index (obesity: OR 1.38, 1.34–1.43 *vs* normal), deprivation status (most deprived: OR 1.09, 1.04–1.14 *vs* least deprived) and Charlson comorbidity index (index ≥5: OR 1.25, 1.16–1.35 *vs* index 0).

Conclusion: Multiple cardiovascular drugs treatment was common in patients with CVD in the UK. High-risk factors of CVD were also associated with cardiovascular polypharmacy. Further studies are warranted to assess the impact of cardiovascular polypharmacy and its interaction on CVD recurrence and mortality.

KEYWORDS

cardiovascular drugs, coronary heart disease, polypharmacy, stroke

The authors confirm that the Principal Investigator for this paper is Li Wei.

1 | INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide, and its prevalence is increasing in line with the ageing population. Coronary heart disease (CHD) and stroke are the most common CVD conditions and are the top two causes of death globally.[1] According to the UK Heart and Circulatory Disease Statistics 2019, adults aged 45 years and above accounted for the majority of overall cardiovascular mortality (approximately 98.5%).[2] Polypharmacy refers to the current use of multiple medications by one individual.[3] Cardiovascular conditions always appear to be the main contributions to polypharmacy. A Scottish study on polypharmacy found that the mean number of medications for patients with only one condition of ischaemic heart disease is 3.7, and 8.0 for patients with ischaemic heart disease and other co-conditions.[4] Historically, polypharmacy has been considered negatively, but it is now increasingly recognised to be necessary and beneficial in patients with some chronic disease (e.g. cardiovascular disease) if polypharmacy is well managed. Currently, only a few studies have reported the prescribing patterns of cardiovascular drugs.[5–7] These studies only investigated limited classes of cardiovascular drugs, rather than providing a comprehensive overview of utilisation pattern. A UK study indicated that cardiovascular risk factors influenced general practitioners' decision to prescribe statins and antihypertensive drugs.[8] However, it is unclear whether these factors are associated with the prescribing of multiple medications. This study aimed to investigate the initial prescription patterns of cardiovascular drugs in UK primary care, and the association between potential risk factors and cardiovascular polypharmacy in patients aged 45 years old and above following their first records of coronary heart disease or stroke.

What is already known about this subject

- Concurrent use of different cardiovascular drugs is common in patients with CVD.
- An appropriate number of CVD drugs (i.e. cardiovascular polypharmacy) is necessary and beneficial in patients with CVD.
- A few CVD drug utilisation studies from the literature focused only on CVD drug classifications rather than the number of CVD drugs.

What this study adds

- This study provides a comprehensive overview of CVD drug patterns (including drug numbers and classifications) in UK patients with new diagnoses of coronary heart disease or stroke.
- Two-fifths of the cardiovascular patients had cardiovascular polypharmacy defined as concurrent use of five or more CVD drugs.
- Male, younger age, currently smoking, higher deprivation score, history of hypertension, hyperlipidaemia, and multiple comorbidities were associated with the increased use of cardiovascular polypharmacy.

2 | METHODS

2.1 | Data source

The Health Improvement Network (THIN) database is a primary care clinical database which includes anonymised data from general practices across the UK. The database includes over 16 million patients from over 744 general practices. In 2013, the active patients in THIN represented approximately 6% of the UK population.[9] THIN includes information for each individual on demographics, diagnoses, prescriptions, referrals, laboratory tests, immunisations and local area deprivation (Townsend score).[10] THIN data have been used previously to study acute cardiovascular events.[11]

Ethics approval was obtained from the THIN Scientific Review Committee (SRC), protocol reference: SRC 17THIN100.

2.2 | Study patients

The study included patients with the first general practitioner (GP) record of CVD between January 2007 and December 2016. CVD was defined based on Read Codes for CHD (myocardial infarction (MI) and angina) and stroke (haemorrhagic stroke, ischaemic stroke and transient ischaemic attacks [TIA]). Patients were divided into groups (CHD and stroke groups) according to their first record of CVD. Other inclusion criteria were patients aged 45 or above at their first diagnosis of CVD and patients had been registered for at least three years in THIN before their first diagnosis of CVD. We excluded patients who died within the first 90 days following the initial cardiovascular event, because their clinical data and prescription information may not be recorded between the first diagnosis and death.

2.3 | Initial treatment

In this study, initial pharmacotherapy with cardiovascular drugs in each patient was defined according to the cardiovascular drugs prescribed during the first 90-day window after the first recorded CVD diagnosis. In the UK, repeat prescriptions are usually issued by primary care physicians for chronic conditions. The prescription interval is usually 28 or 56 days. Our study included CV drugs with a prescription duration ≥ 28 days or with at least two prescriptions during the 90-day exposure window. This was to make sure drugs

were prescribed for long-term use. Patients were also categorised into groups according to the specific number or combination of drugs prescribed. Cardiovascular drugs were identified from the British National Formulary (BNF) Chapter two (cardiovascular system). Compound medicines are separated into individual drug constituents.

2.4 | Data extraction and missing data

Information on demographics, clinical characteristics and cardiovascular prescriptions were extracted from the THIN database. Baseline characteristics included age, gender, smoking status, alcohol consumption, body mass index (BMI), blood pressure (BP), total cholesterol (TC), Townsend score, and comorbidities during the 1-year window prior to the first cardiovascular event.

Missing data for each baseline characteristic were coded as a separate category.

2.5 | Statistical analysis

All analyses were performed using SAS software version 9.4. Data were presented as mean (standard deviation [SD]) for continuous variables and as frequency (%) for categorical variables. Comparisons were performed using student's *t*-test for continuous variables, and the chi-squared test for categorical variables between the CHD and stroke patients.

The study examined the percentage of CVD drugs prescribed by the numbers of drugs (0, 1, 2, 3, 4, 5, 6, ≥7) issued during the first 90 days following the diagnosis of CVD stratified by age (10-year age groups up to ≥85 years), gender, smoking status (never smoked, current smoker, ex-smoker), BMI (mean, normal, overweight, obese and underweight), blood pressure (normal, stage 1, 2 and 3 hypertension and hypotension), total cholesterol (optimal, intermediate and high), Charlson comorbidity index (excluding myocardial infarction and cerebrovascular disease), history of percutaneous transluminal coronary intervention (PCI), hypertension, hyperlipidaemia, arrhythmia, heart failure (HF), dementia, diabetes, chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis (RA) or chronic kidney disease (CKD), and area deprivation status (Townsend score 1–5).

The average number and the percentage of patients with different numbers of CVD drugs in each calendar year were calculated. The proportion of patients prescribed with the most commonly used classes and combinations of CV drugs during the study period was also investigated.

Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were evaluated by logistic regression model to examine the association between baseline characteristics and CV polypharmacy (prescribing of ≥5 CV drugs). All two-sided *P*-values less than 0.05 were considered to be statistically significant.

3 | RESULTS

3.1 | Patient characteristics

From 2007 to 2016, 121,600 patients aged 45 years and above were diagnosed with CVD. The study included 59,843 patients with CHD (25,266 patients with angina and 34,577 patients with MI) and 61,757 patients with stroke. Patient characteristics at their first CVD are presented in Table 1. The mean patient age at CV events was 69.3 ± 11.7 years (67.0 ± 11.4 years for CHD patients and 71.7 ± 11.5 years for stroke patients). The proportion of male patients with CVD was 55.5% (62.0% for CHD patients and 48.6% for stroke patients).

3.2 | Usage of cardiovascular drugs

Figure 1 shows the percentage of patients receiving different numbers of CV drugs after their first CVD events. Overall, 11.0% of CVD patients had prescriptions for zero or one long-term used CV drug, 29.8% were receiving two or three regular drugs, 38.6% were receiving four or five drugs, and 20.5% were receiving six or more CV drugs. The percentage of patients with CVD receiving cardiovascular polypharmacy (≥5 CV drugs) was 40.6%. The average number of CV drugs was 3.9 (SD: 1.9) in overall patients with CVD, 4.8 (SD: 1.8) in patients with CHD, and 3.1 (SD: 1.7) in patients with stroke, respectively. The majority of patients with CHD received five or more drugs (61.1%). By contrast, patients with stroke received fewer CV drugs; 62.5% were receiving two to four drugs.

Overall, in CVD patients, the most commonly prescribed CV drugs were aspirin (59.9%), simvastatin (48.0%), clopidogrel (39.8%), bisoprolol (34.5%), ramipril (30.5%) and atorvastatin (28.3%) (Supporting Information Figure S1). In CHD patients, aspirin (79.0%), bisoprolol (59.6%), clopidogrel (45.6%), ramipril (45.0%), simvastatin (44.2%) and atorvastatin (38.6%) were frequently issued. In stroke patients, simvastatin (51.8%), aspirin (41.4%), clopidogrel (34.3%), amlodipine (18.4%), atorvastatin (18.4%) and ramipril (16.6%) were commonly prescribed drugs.

Among patients with CHD, the most commonly used classes of CV drugs were antiplatelet drugs (84.9%), lipid-regulating drugs (85.3%), β-blockers (73.1%), angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blocker (ARBs) (67.7%) and antianginal drugs (30.2%). Dual antiplatelet therapy was prescribed to 48.2% of CHD patients. However, the proportions of dual antiplatelet therapy and ACEIs/ARBs were 72.0% and 82.1% in patients with MI. In patients with stroke or TIA, the most frequently prescribed CV drugs were antiplatelet drugs (72.3%), lipid-regulating drugs (72.3%), ACEIs/ARBs (43.8%), calcium-channel blockers (CCBs) (27.5%) and diuretics (26.4%) (Figure 2). Prescribing for patients with MI and angina are shown separately in Supporting Information Figure S2.

Details of specific combinations of the top five commonly used classes of cardiovascular drugs in CHD and stroke patients are

TABLE 1 Characteristics of the study population at their first CVD

Characteristics	Total (*n* = 121,600)	CHD (*n* = 59,843)	Stroke (*n* = 61,757)	*P*-value
Male (%)	67,073 (55.2)	36,894 (61.7)	30,179 (48.9)	<0.01
Age, mean ± SD, years	69.5 ± 11.9	67.2 ± 11.5	71.8 ± 11.7	<0.01
Age groups, years (%)				
45–54	15,370 (12.6)	9,540 (15.9)	5,830 (9.4)	<0.01
55–64	27,427 (22.6)	16,235 (27.1)	11,192 (18.1)	
65–74	34,262 (28.2)	17,119 (28.6)	17,143 (27.8)	
75–84	31,134 (25.6)	12,517 (20.9)	18,617 (30.2)	
85 and older	13,407 (11.0)	4,432 (7.4)	8,975 (14.5)	
Smoking status (%)				
Non-smoker	53,094 (43.7)	24,438 (40.8)	28,656 (46.4)	<0.01
Current smoker	24,679 (20.3)	13,195 (22.1)	11,483 (18.6)	
Ex-smoker	41,025 (33.7)	21,287 (35.6)	19,737 (32.0)	
Missing	2,803 (2.3)	923 (1.5)	1,880 (3.1)	
Alcohol consumption (%)				
Non-drinker	18,767 (15.4)	9,143 (15.3)	9,624 (15.6)	<0.01
Current drinker	66,108 (54.4)	34,390 (57.5)	31,718 (51.4)	
Ex-drinker	4,280 (3.5)	2,136 (3.6)	2,144 (3.5)	
Missing	32,445 (26.7)	14,174 (23.7)	18,271 (29.6)	
BMI, mean ± SD	27.9 ± 5.3	28.2 ± 5.2	27.5 ± 5.3	<0.01
BMI groups (%)				
Normal (18.5–24.9 kg/m^2)	29,160 (24.0)	13,151 (22.0)	16,009 (25.9)	<0.01
Overweight (25.0–29.9 kg/m^2)	41,148 (33.8)	21,517 (36.0)	19,631 (31.8)	
Obesity (≥ 30.0 kg/m^2)	31,061 (25.5)	16,885 (28.2)	14,176 (23.0)	
Underweight (< 18.5 kg/m^2)	1,932 (1.6)	739 (1.2)	1,193 (1.9)	
Missing	18,299 (15.1)	7,551 (12.6)	10,748 (17.4)	
BP status (%)				
Normal (BP < 140/90 mmHg)	40,689 (39.0)	21,539 (39.8)	19,150 (38.2)	<0.01
Stage 1 hypertension (BP ≥ 140/90 mmHg)	31,458 (30.2)	15,944 (29.5)	15,514 (30.9)	
Stage 2 hypertension (BP ≥ 160/100 mmHg)	10,371 (10.0)	4,900 (9.1)	5,471 (10.9)	
Stage 3 hypertension (systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg)	4,312 (4.1)	1,713 (3.2)	2,599 (5.2)	
Hypotension (BP < 90/60 mmHg)	157 (0.2)	101 (0.2)	56 (0.1)	
Missing	17,276 (16.6)	9,878 (18.3)	7,398 (14.7)	
TC status (%)				
Optimal (<5.2 mmol/L)	48,685 (40.0)	23,624 (39.5)	25,061 (40.6)	<0.01
Intermediate (5.3–6.2 mmol/L)	30,403 (25.0)	14,983 (25.0)	15,420 (25.0)	
High (>6.2 mmol/L)	19,460 (16.0)	10,342 (17.3)	9,118 (14.8)	
Missing	23,052 (19.0)	10,894 (18.2)	12,158 (19.7)	
Townsend score (%)				
1 (least deprived)	25,088 (20.6)	11,958 (20.0)	13,130 (21.3)	<0.01
2	24,957 (20.5)	12,245 (20.5)	12,712 (20.6)	
3	23,234 (19.1)	11,438 (19.1)	11,796 (19.1)	
4	20,126 (16.6)	10,024 (16.8)	10,102 (16.4)	
5 (most deprived)	14,240 (11.7)	7,310 (12.2)	6,930 (11.2)	
Missing	13,955 (11.5)	6,868 (11.5)	7,087 (11.5)	

TABLE 1 (Continued)

Characteristics	Total (*n* = 121,600)	CHD (*n* = 59,843)	Stroke (*n* = 61,757)	*P*-value
Charlson comorbidity index (%)				
0	59,272 (48.7)	29,492 (49.3)	29,780 (48.2)	<0.01
1	29,763 (24.5)	14,740 (24.6)	15,023 (24.3)	
2	13,481 (11.1)	6,263 (10.5)	7,218 (11.7)	
3	10,953 (9.0)	5,383 (9.0)	5,570 (9.0)	
4	4,785 (3.9)	2,372 (4.0)	2,413 (3.9)	
≥5	3,346 (2.8)	1,593 (2.7)	1,753 (2.8)	
History or PCI (%)	6,426 (6.2)	6,182 (11.4)	237 (0.5)	<0.01
Comorbidity (%)				
Hypertension	64,631 (53.2)	29,798 (49.8)	34,833 (56.4)	<0.01
Hyperlipidaemia	19,242 (15.8)	10,164 (17.0)	9,078 (14.7)	<0.01
Arrhythmia	14,847 (12.2)	5,430 (9.1)	9,417 (15.3)	<0.01
Heart failure	6,992 (5.8)	4,379 (7.3)	2,613 (4.2)	<0.01
Dementia	2,869 (2.4)	664 (1.1)	2,205 (3.6)	<0.01
Diabetes	20,734 (17.1)	10,423 (17.4)	10,311 (16.7)	<0.01
COPD	10,417 (8.6)	5,175 (8.7)	5,242 (8.5)	0.32
Asthma	16,705 (13.7)	8,469 (14.2)	8,236 (13.3)	<0.01
RA	2,540 (2.1)	1,265 (2.1)	1,275 (2.1)	0.55
CKD	21,258 (17.5)	9,428 (15.8)	11,830 (19.2)	<0.01

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; OR, odds ratio; PCI, percutaneous transluminal coronary intervention; RA, rheumatoid arthritis; TC, total cholesterol.

FIGURE 1 Percentage of patients receiving different numbers of CV drugs

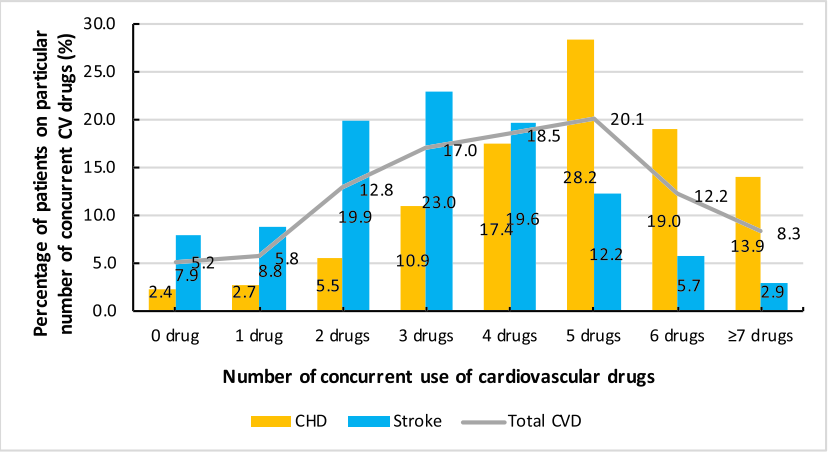
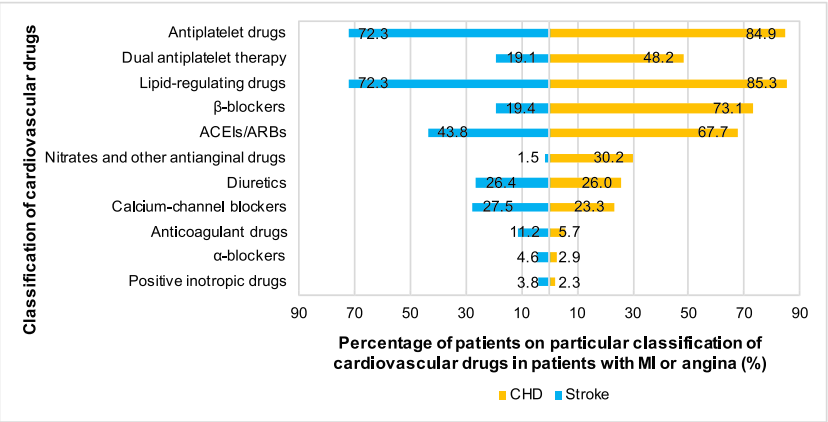


FIGURE 2 Percentage of patients receiving particular classifications of CV drugs in separate disease groups between 2007 and 2016



presented in Table 2. Of the 59,843 patients with CHD, 4,896 (8.2%) received none or one prescription of antiplatelet drugs, lipid-regulating drugs, β-blockers, ACEIs/ARBs or antianginal drugs. The majority of CHD patients were prescribed a combination of three (23.2%) or four (44.1%) drug classes. The combined use of antiplatelet drugs, lipid-regulating drugs, β-blockers and ACEIs/ARBs (34.3%) was most frequently prescribed in CHD patients. In 61,757 patients with stroke, 5,841 (9.5%) patients received none of antiplatelet drugs, lipid-regulating drugs, ACEIs/ARBs, CCBs or diuretics. The percentage of stroke patients received one, two and three of the five classes of CV drugs was 13.0%, 29.0% and 27.4%, respectively. The combinations of antiplatelet drugs and lipid-regulating drugs (18.6%), and the

TABLE 2 Combinations of the top five classes of CV drugs prescribed in patients with CHD and stroke

CHD (*n* = 59,843)			Stroke (*n* = 61,757)		
CV drugs	**Frequency**	**%**	**CV drugs**	**Frequency**	**%**
None of the five class drugs	1,927	3.2	**None of the five class drugs**	5,841	9.5
One class	2,969	5.0	**One class**	8,043	13.0
APDs	844	1.4	APDs	3,515	5.7
LRDs	800	1.3	LRDs	2,560	4.2
BBs	563	0.9	ACEIs/ARBs	843	1.4
ACEIs/ARBs	466	0.8	CCBs	562	0.9
AADs	296	0.5	DRs	563	0.9
Two combination	6,444	10.8	**Two combination**	17,911	29.0
APDs + LRDs	2,100	3.5	APDs + LRDs	11,487	18.6
APDs + BBs	898	1.5	APDs + ACEIs/ARBs	1,053	1.7
APDs + ACEIs/ARBs	543	0.9	APDs + CCBs	692	1.1
APDs + AADs	372	0.6	APDs + DRs	744	1.2
LRDs + BBs	855	1.4	LRDs + ACEIs/ARBs	1,528	2.5
LRDs + ACEIs/ARBs	684	1.1	LRDs + CCBs	714	1.2
LRDs + AADs	257	0.4	LRDs + DRs	559	0.9
BBs + ACEIs/ARBs	423	0.7	ACEIs/ARBs + CCBs	446	0.7
BBs + AADs	164	0.3	ACEIs/ARBs + DRs	487	0.8
ACEIs/ARBs + AADs	148	0.3	CCBs + DRs	201	0.3
Three combination	13,894	23.2	**Three combination**	16,905	27.4
APDs + LRDs + BBs	5,262	8.8	APDs + LRDs + ACEIs/ARBs	7,667	12.4
APDs + LRDs + ACEIs/ARBs	3,728	6.2	APDs + LRDs + CCBs	3,397	5.5
APDs + LRDs + AADs	1,284	2.2	APDs + LRDs + DRs	2,076	3.4
APDs + BBs + ACEIs/ARBs	996	1.7	APDs + ACEIs/ARBs + CCBs	507	0.8
APDs + ACEIs/ARBs +AADs	413	0.7	APDs + ACEIs/ARBs + DRs	776	1.3
APDs + BBs + AADs	236	0.4	APDs + CCBs +DRs	285	0.5
LRDs + BBs + ACEIs/ARBs	1,180	2.0	LRDs + ACEIs/ARBs + CCBs	747	1.2
LRDs + BBs + AADs	368	0.6	LRDs + ACEIs/ARBs + DRs	942	1.5
LRDs + ACEIs/ARBs + AADs	288	0.5	LRDs + CCBs + DRs	275	0.5
BBs + ACEIs/ARBs + AADs	139	0.2	ACEIs/ARBs + CCBs + DRs	233	0.4
Four combination	26,382	44.1	**Four combination**	10,264	16.6
APDs + LRDs + BBs + ACEIs/ARBs	20,495	34.3	APDs + LRDs + ACEIs/ARBs + CCBs	3,912	6.3
APDs + LRDs + BBs + AADs	2,906	4.9	APDs + LRDs + ACEIs/ARBs + DRs	4,131	6.7
APDs + LRDs + ACEIs/ARBs + AADs	2,115	3.5	APDs + LRDs + CCBs + DRs	1,261	2.0
APDs + BBs + ACEIs/ARBs + AADs	400	0.7	APDs + ACEIs/ARBs + CCBs + DRs	351	0.6
LRDs + BBs + ACEIs/ARBs + AADs	466	0.8	LRDs + ACEIs/ARBs + CCBs + DRs	609	1.0
Five combination	8,227	13.8	**Five combination**	2,793	4.5
APDs + LRDs + BBs + ACEIs/ARBs + AADs	8,227	13.8	APDs + LRDs + ACEIs/ARBs + CCBs + DRs	2,793	4.5

AADs, antianginal drugs; ACEIs, angiotensin-converting enzyme inhibitors; APDs, antiplatelet drugs; ARBs, angiotensin receptor blockers; BBs, β-blockers; CCBs, calcium channel blockers; CHD, coronary heart disease; CV, cardiovascular; DRs, diuretics; LRDs, lipid-regulating drugs.

combination of antiplatelet drugs, lipid-regulating drugs and ACEIs/ARBs (12.4%) were frequently prescribed to patients with stroke.

3.3 | Trends in initial therapy for secondary prevention 2007–2016

Figure 3 shows the trends in the number of cardiovascular drugs issued to CVD patients from 2007 to 2016. From 2010 the percentage of patients receiving two drugs increased from 10.9% in 2010 to 15.8% in 2016. Conversely, the percentage of patients receiving six drugs (from 13.0% to 10.8%) and seven or more drugs (from 8.9% to 7.0%) showed a declining trend from 2010 to 2016. When investigating the trends in CHD and stroke separately, the CV drug usage remained stable (Supporting Information Figures S3 and S4).

3.4 | Factors associated with cardiovascular polypharmacy

Figure 4 shows the proportion of patients receiving different numbers of cardiovascular drugs and the mean number of cardiovascular drugs by the risk factor groups. Table 3 summarises the potential factors predicting the probability of cardiovascular polypharmacy. Women were less likely to be issued with five or more cardiovascular drugs (OR: 0.74, 95% CI: 0.72–0.76). Patients receiving cardiovascular polypharmacy decreased with increasing age (OR = 0.94, 0.81, 0.69 and 0.50 in patients aged 55–64, 65–74, 75–84 and 85 + years old, respectively, *vs* patients aged 45–54 years old). Current smokers were more likely to be receiving cardiovascular polypharmacy with an OR of 1.19 (95% CI: 1.15–1.24). High BMI was shown to be associated with cardiovascular polypharmacy as overweight patients (OR = 1.23, 95% CI: 1.19–1.27) and obese patients (OR = 1.38, 95% CI: 1.34–1.43) were significantly more likely to be prescribed five or more cardiovascular drugs. Compared to patients with normal blood pressure, the ORs were 1.06 (95% CI: 1.03–1.09), 1.08 (95% CI: 1.04–1.13) and 1.24 (95% CI: 1.17–1.32) for patients with stage 1, stage 2 and stage 3 hypertension, respectively. The area deprivation status was associated with polypharmacy. Compared with patients living in the least deprived area, the ORs of cardiovascular polypharmacy increased with higher deprived areas (OR = 1.05 and 1.06 in patients assigned a Townsend score of four and five, respectively). The probability of receiving cardiovascular polypharmacy in patients with a history of PCI was 5.26 times (95% CI: 4.96–5.58) compared to patients with no history. High Charlson comorbidity index (CCI) was also a predictive factor of cardiovascular polypharmacy with ORs of 1.22 (95% CI: 1.17–1.28), 1.31 (95% CI: 1.23–1.40) and 1.25 (95% CI: 1.16–1.35) in CCIs of three, four and five or more, respectively. CVD patients with hypertension (OR: 2.03, 95% CI: 1.97–2.08), hyperlipidaemia (OR: 1.16, 95% CI: 1.12–1.20), heart failure (OR: 2.57, 95% CI: 2.43–2.71), diabetes (OR: 1.25, 95% CI: 1.21–1.29), chronic kidney disease (OR: 1.19, 95% CI: 1.16–1.24) and arrhythmia (OR: 1.05, 95% CI: 1.01–1.10) were more likely to be issued with five or more CV drugs. Conversely, having a history of dementia (OR: 0.44, 95% CI: 0.40–0.49), COPD (OR: 0.92, 95% CI: 0.88–0.97) or asthma (OR: 0.90, 95% CI: 0.87–0.93) decreased the probability of CV polypharmacy.

4 | DISCUSSION

Although there are studies on drug utilisation for cardiovascular disease, this is the first UK study to provide a comprehensive overview of initial prescription patterns of cardiovascular drugs and investigate potential factors associated with the probability of cardiovascular polypharmacy in patients with new diagnoses of coronary heart disease or stroke. Our results found that 40.6% of patients with CVD received cardiovascular polypharmacy. The average number of cardiovascular drugs was 4.8 in patients with CHD and 3.1 in patients with stroke. Male, younger age, current smoking, high BMI, hypertension, hyperlipidaemia, higher deprivation score and multiple comorbidities were associated with an increased likelihood of receiving cardiovascular polypharmacy.

Antiplatelet therapy, statins, ACEIs and beta-blockers are recommended for all patients for the secondary prevention of MI.[12–15] We observed high rates of antiplatelet drugs (91.8%), lipid-regulating drugs (89.8%), ACEIs/ARBs (82.1%) and β-blockers (80.2%) in patients with MI. The proportion of patients prescribed

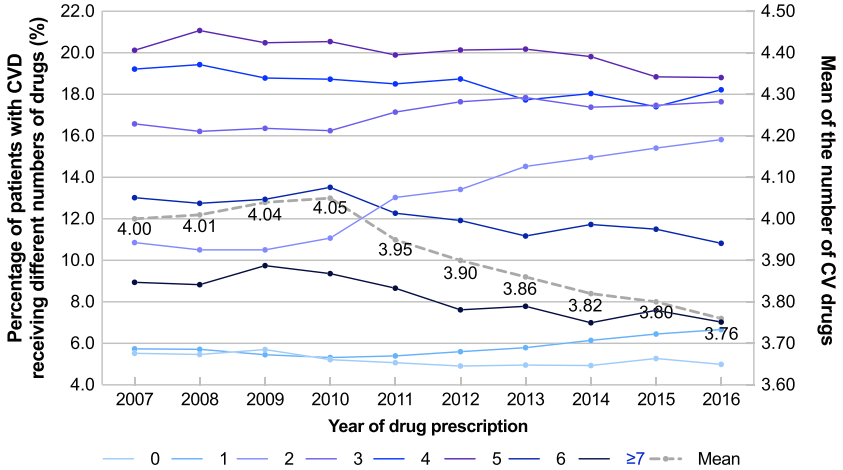


FIGURE 3 Trends in numbers and means of the number of CV drugs prescribed to patients with CVD from 2007 to 2016

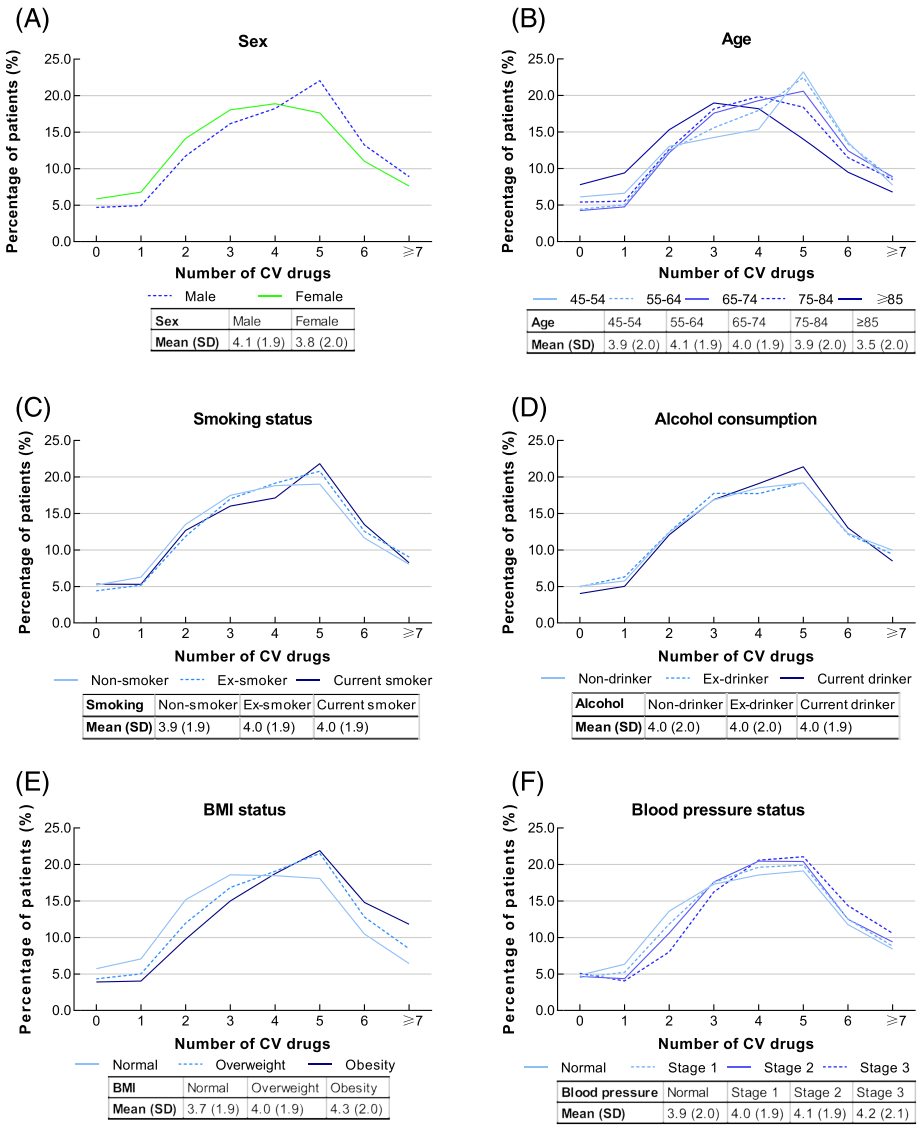


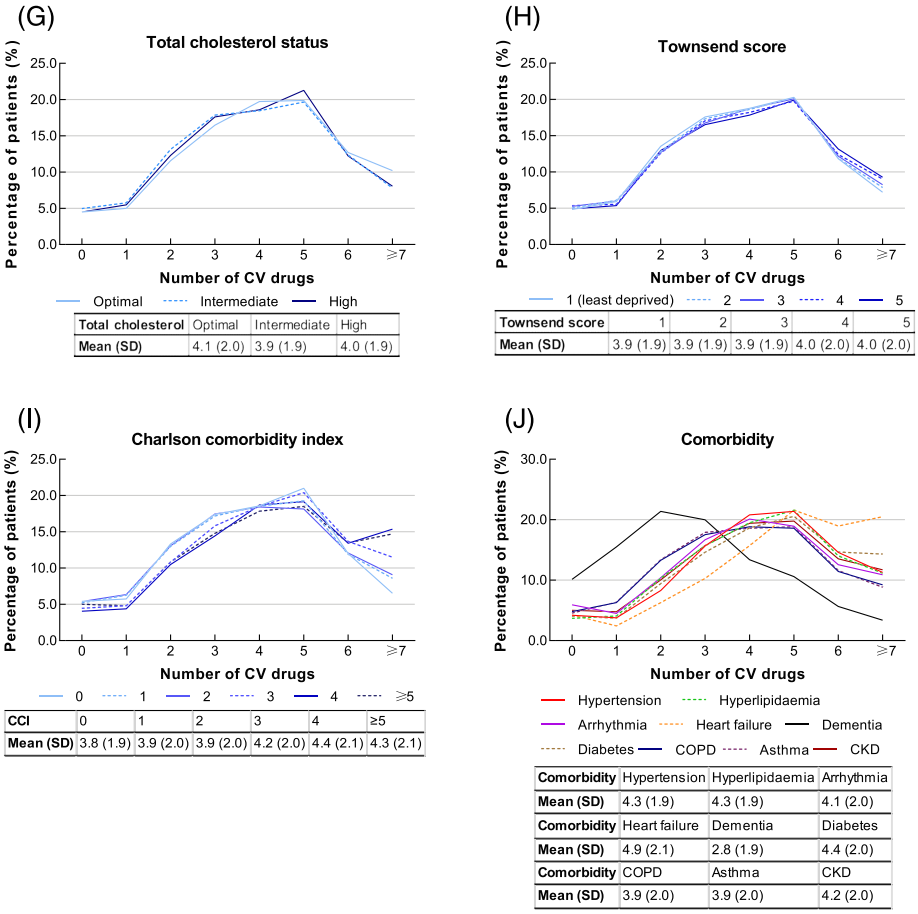
FIGURE 4 Percentage of patients receiving different numbers of CV drugs by (A) sex, (B) age, (C) smoking status, (D) alcohol assumption, (E) BMI status, (F) blood pressure status, (G) total cholesterol status, (H) Townsend score, (I) Charlson comorbidity index and (J) comorbidities

with dual antiplatelet (72.0%) therapy was relatively lower. In patients with stroke, over 75% of stroke patients initially received at least one of antiplatelet drugs and lipid-regulating drugs. ACEIs/ARBs (43.8%), CCBs (27.5%) and diuretics (26.4%) were also frequently issued. Guidelines state that blood pressure therapy is indicated for the secondary prevention of stroke in patients who have a sustained BP ≥ 140 mmHg systolic or ≥90 mmHg diastolic, and ACEIs/ARBs, CCBs and diuretics are the first-line antihypertensive drugs.[16] Our results indicated that the usage of cardiovascular drugs in "real-world" patients still suboptimally adhered to the guideline recommendations.

Between 2007 and 2016, the initial use of cardiovascular drugs for the secondary prevention of CVD remained stable. This trend is not surprising because ACEIs, aspirin, β-blockers and statins were advocated to reduce mortality after acute MI in the NICE guidelines published in 2001,[17] which was consistent with the latest version.[15] Similarly, the first-line pharmacotherapy for stroke and TIA recommended in the latest NICE guidelines was in accordance with the guidelines published in 2008.[12,18]

We further investigated the association between the prescribing of cardiovascular polypharmacy and potential risk factors at baseline. In our analysis, women were less likely to have cardiovascular polypharmacy. Several studies have reported underuse of cardiovascular drugs in women after their first diagnosis of CVD.[5–7,19] The AusHEART study[19] reported that women were more likely to be underestimated by physicians on the true risk of cardiovascular disease. A previous study conducted in the UK has also suggested that women were less likely to be systematically screened for cardiovascular disease than men.[20] These might partially explain the gender difference in cardiovascular drug prescribing.

In accordance with current evidence, the results of this study found a lower rate of cardiovascular polypharmacy in older patients.[5,21,22] One potential reason could be that combination



Total cholesterol	Optimal	Intermediate	High
Mean (SD)	4.1 (2.0)	3.9 (1.9)	4.0 (1.9)

Townsend score	1	2	3	4	5
Mean (SD)	3.9 (1.9)	3.9 (1.9)	3.9 (1.9)	4.0 (2.0)	4.0 (2.0)

CCI	0	1	2	3	4	≥5
Mean (SD)	3.8 (1.9)	3.9 (2.0)	3.9 (2.0)	4.2 (2.0)	4.4 (2.1)	4.3 (2.1)

Comorbidity	Hypertension	Hyperlipidaemia	Arrhythmia
Mean (SD)	4.3 (1.9)	4.3 (1.9)	4.1 (2.0)
Comorbidity	Heart failure	Dementia	Diabetes
Mean (SD)	4.9 (2.1)	2.8 (1.9)	4.4 (2.0)
Comorbidity	COPD	Asthma	CKD
Mean (SD)	3.9 (2.0)	3.9 (2.0)	4.2 (2.0)

FIGURE 4 (Continued)

therapy may be a less cost-effective regimen for older patients because of a longer recovery period and shorter life expectancy.[23] In addition, for older patients, multiple factors like drug interactions and potential adverse effects have to be considered, which may lead to an underuse of drug therapies.[24,25] Current smoking, high body mass index, high blood pressure and hyperlipidaemia were shown to be considerably and positively associated with initiating cardiovascular polypharmacy, which might be attributable to awareness of the increased risk of cardiovascular disease. CVD patients with a history of PCI were more likely to be treated with five or more cardiovascular drugs, which might be related to higher severity of disease condition or additional medications prescribed as a result of intervention, e.g. stenting.

Multi-comorbidities were also presented as a risk factor of cardiovascular polypharmacy. CVD patients with a history of heart failure, diabetes or chronic kidney disease often receive combination therapy more frequently. In addition to the drugs for the secondary prevention of CHD or stroke, guidelines recommend that those patients with HF should be prescribed some other cardiovascular drugs. For example, mineralocorticoid receptor antagonists are indicated for patients who have HF with reduced ejection fraction and continue to have symptoms of HF. Anticoagulant drugs combined with antiplatelet drugs may be recommended for patients with stroke and HF.[26] Diabetes is a significant risk factor of cardiovascular disease, so it would be expected that doctors may prescribe additional cardiovascular drugs for those CVD patients with diabetes. Many significant CVD risk factors including diabetes, hypertension and dyslipidaemia are highly prevalent in patients with CKD.[27] The guidelines indicate that CKD patients should aim to control their blood pressure below 140/90 mmHg and lower than 130/80 mmHg if they also have diabetes.[28] Therefore, CVD patients with CKD may be prescribed more cardiovascular drugs. In contrast, patients with a history of dementia were less likely to be prescribed more than five cardiovascular drugs. The reason for the underuse of cardiovascular drugs in dementia is uncertain. NICE guidelines suggest that some commonly used drugs may cause cognitive impairment, which might be a concern for doctors prescribing for patients who have CVD and dementia.[29] Our results showed that patients with asthma also received cardiovascular polypharmacy less frequently, which might be due to concerns about drug interactions as β-blockers have been debated for many years to be contraindicated in asthma patients.[30] In addition, this study showed that high deprivation status was associated with cardiovascular polypharmacy. This is probably attributed to a poorer level of health associated with social deprivation. This finding is similar to the result of a Scottish study.[31]

Polypharmacy has historically been considered negatively because of the associated risk of adverse events and decreased adherence.[32,33] It is now accepted that in many chronic conditions, polypharmacy is

TABLE 3 Odds ratios for factors associated with cardiovascular polypharmacy

Variables	Univariable OR (95% CI)	Multivariable OR (95% CI)
Gender		
Male	1 (reference)	1 (reference)
Female	0.72 (0.70–0.74)	0.74 (0.72–0.76)
Age group (years)		
45–54	1 (reference)	1 (reference)
55–64	1.00 (0.96–1.04)	0.94 (0.90–0.98)
65–74	0.90(0.86–0.93)	0.81 (0.78–0.85)
75–84	0.77 (0.75–0.81)	0.69 (0.66–0.72)
85 and over	0.54 (0.52–0.57)	0.50 (0.47–0.53)
Smoking status		
Non-smoker	1 (reference)	1 (reference)
Ex-smoker	1.17 (1.14–1.20)	1.09 (1.06–1.12)
Current smoker	1.22 (1.18–1.26)	1.19 (1.15–1.24)
Alcohol status		
Non-drinker	1 (reference)	1 (reference)
Ex-drinker	0.98 (0.91–1.04)	0.88 (0.82–0.94)
Current drinker	1.06 (1.03–1.10)	0.98 (0.94–1.01)
BMI group		
Normal	1 (reference)	1 (reference)
Overweight	1.39 (1.35–1.43)	1.23 (1.19–1.27)
Obese	1.75 (1.70–1.81)	1.38 (1.34–1.43)
Underweight	0.63 (0.57–0.70)	0.73 (0.66–0.82)
BP status		
Normal	1 (reference)	1 (reference)
Stage 1 hypertension	1.08 (1.05–1.11)	1.06 (1.03–1.09)
Stage 2 hypertension	1.13 (1.09–1.18)	1.08 (1.04–1.13)
Stage 3 hypertension	1.32 (1.24–1.40)	1.24 (1.17–2.05)
TC status		
Optimal	1 (reference)	1 (reference)
Intermediate	0.89 (0.86–0.91)	1.02 (0.99–1.05)
High	0.95 (0.92–0.98)	1.13 (1.09–1.17)
Townsend score		
1 (least deprived)	1 (reference)	1 (reference)
2	1.03 (0.99–1.07)	1.03 (0.99–1.06)
3	1.05 (1.01–1.09)	1.03 (0.99–1.07)
4	1.08 (1.04–1.12)	1.05 (1.00–1.09)
5 (most deprived)	1.13 (1.09–1.18)	1.06 (1.04–1.14)
Charlson comorbidity index		
0	1 (reference)	1 (reference)
1	1.01 (0.98–1.04)	1.01 (0.98–1.04)
2	0.99 (0.95–1.03)	1.05 (1.01–1.09)
3	1.28 (1.23–1.33)	1.22 (1.17–1.28)
4	1.41 (1.33–1.49)	1.31 (1.23–1.40)
≥5	1.34 (1.25–1.44)	1.25 (1.16–1.35)
History of PCI	4.73 (4.47–5.00)	5.26 (4.96–5.58)

TABLE 3 (Continued)

Variables	Univariable OR (95% CI)	Multivariable OR (95% CI)
Comorbidity		
Hypertension	1.41 (1.38–1.45)	2.03 (1.97–2.08)
Hyperlipidaemia	1.16 (1.12–1.20)	1.16 (1.12–1.20)
Arrhythmia	1.09 (1.05–1.12)	1.05 (1.01–1.10)
Heart failure	2.41 (2.29–2.53)	2.57 (2.43–2.71)
Dementia	0.35 (0.32–0.38)	0.44 (0.40–0.49)
Diabetes	1.55 (1.50–1.59)	1.25 (1.21–1.29)
COPD	0.94 (0.90–0.98)	0.92 (0.88–0.97)
Asthma	0.94 (0.90–0.97)	0.90 (0.87–0.93)
Chronic kidney disease	1.24 (1.21–1.28)	1.19 (1.16–1.24)
RA	0.98 (0.90–1.07)	1.08 (0.99–1.17)

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; OR, odds ratio; PCI, percutaneous transluminal coronary intervention; RA, rheumatoid arthritis; TC, total cholesterol.

also therapeutically beneficial. Prescribing of appropriate multiple cardiovascular drugs is necessary for these with high risk of recurrent CV events. Our previous systematic review and meta-analysis study assessed the effectiveness of evidence-based combination pharmacotherapy (EBCP) and found that EBCP is associated with a decreased risk of all-cause mortality and cardiovascular events in patients with cardiovascular disease.[34] However, our results found that underuse of evidence-based pharmacotherapy still existed in patients with cardiovascular disease (5.2% of individuals did not receive routine CV medications and 5.8% only received one medication following their initial CV events), and this finding was consistent with previous studies.[35,36] The high proportions of non-smokers and patients without comorbidities in this group may partially explain the phenomenon of underuse of CVD drugs. The result indicated that cardiovascular risk factors may influence general practitioners' decision to prescribe cardiovascular drugs.[8] Evidence-based recommendations on personalised medicine are still limited. Further studies are required to evaluate the risk and benefit of cardiovascular polypharmacy when prescribing for the prevention and treatment of cardiovascular disease.

4.1 | Strengths and limitations

Our study has several strengths. It used a large UK primary care data source which is representative of the UK general population. The analysis has provided comprehensive details about the patterns of initial cardiovascular pharmacotherapy prescribing by primary physicians in patients with coronary heart disease and stroke.

Our study also has limitations. Firstly, the dataset only provides records of prescriptions; therefore, it was not possible to determine if drugs were actually dispensed, taken or adequately used by patients. However, as the current study aimed to describe the utilisation patterns of CV drugs after the CV event, this will not affect our results. Secondly, because the THIN database does not capture data from hospital treatment and over-the-counter (OTC) drugs (e.g., aspirin available OTC), the study was not able to address drug usage outside the records from general practice which may lead to an underestimation in the results. This may be important, especially for patients under the age of 60 years who may be liable to pay prescription charges in England.

5 | CONCLUSIONS

Multiple cardiovascular drug treatment was common in CVD patients in the UK. High-risk factors of CVD were associated with cardiovascular polypharmacy. Further studies are warranted to assess the impact of cardiovascular polypharmacy and its interaction on CVD recurrence and mortality.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

L.W. and T.T.M conceived the original idea. T.T.M., I.W. and L.W. designed the study. T.T.M. conducted the study and wrote the first draft of the manuscript. K.M. and W.L. provided statistical advice on the data analysis. C.W., I.S.M. and R.B. critically reviewed the manuscript. All authors participated in the interpretation of the study results and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

No additional data are available for sharing.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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